REMARKS

This paper is filed in response to the Non-Final Office Action dated April 2, 2010, to supplement Applicants' response of June 30, 2010. Claims 8-9, 1-15, 22-23, 26-30, 37-38, 45, 47, and 49-53 are currently pending in this application. The support for the newly added claims 5-53 can be found at least in the original claims.

Reconsideration of the instant application is respectfully requested in view of the amendments above and the following remarks.

1. Interview Summary

Applicant would like to thank the Examiner again for granting a telephonic interview on July 8, 2010. During the interview, Applicant's representative, Roman Fayerberg, and the Examiner discussed the Examiner's reasons for rejection of claims 7, 45, 47 and 49. The Examiner kindly agreed to allow Applicants to supplement their response filed on June 30, 2010. Accordingly, in this supplemental response, Applicants cancel claim 7 and related claims and amend claims 45, 47, and 49 to reflect the Examiner's comments.

2. Rejections under 35 U.S.C § 103

Claims 7-15, 24, 25, 36-40, 44, 45 and 47-49 were rejected under 35 U.S.C. § 103 as being unpatentable over Hair et al. (U.S. Patent 6,521,750) or (U.S. 6, 858,431) in view of Nagahara et al. Claims 7-9, 12-15, 21-23, 26-30, 36-38 were also rejected as obvious over Boden (Endocrinology 1998, 139(12): 5125-5134) in view of Nagahara et al. and van Beuningen et al. (Osteoarthritis and Cartilage, 1998, Vol. 6, pages 306-317), and in further view of Liu et al. (Bone Miner. Res. 17(3): 406-414 (2002)).

The only independent claims currently pending in the instant application are claims 45, 47 and 49. Applicants have amended these claims 45, 47, and 40 to clarify that they encompass fusion peptides which are a combination of a protein transduction domain and an amino acid sequence consisting of SEQ ID NO 1, SEQ ID NO 2, SEQ ID NO 4, SEQ ID NO 7, or SEQ ID NO 8.

Applicants respectfully submit that the cited references fail to disclose any osteoinductive peptides other than full length LMP-1, RLMP, and LMP-1s/LMP-1(t). For example, in the

Office Action mailed on July 14, 2009, recognizing this fact, the Examiner stated as follows in regard to Hair et al:

> However, Hair et al. do not teach a method of inducing bone formation in a mammal or inducing osteoblast differentiation in a progenitor cell comprising administering an effective amount of a fusion polypeptide comprising a protein transduction domain and at least one osteoinductive polypeptide, or an osteoinductive polypeptide that has less than 100% homology to LMP-1, RLMP and LMP-1s. (See ps. 5, 12 of the Office Action)

The specification explains that based on previous work by Applicants, Applicants have surmised that a forty amino acid sequence corresponding to amino acids 94-133 of the amino acid sequence of human LMP-1 common to both LMP-1 and LMP-3, in itself, may potentially have osteoinductive potential1. Applicants have now unexpectedly discovered that peptides that are substantially shorter than the amino acid sequence corresponding to amino acids 94-133 of the amino acid sequence of human LMP-1 (hLMP-1) still have osteoinductive potential. This clearly could not be expected from the prior art.

As shown in Fig. 6, peptides represented by SEQ. ID. NOs 1-8 have varying degree of osteoinductive activity. For example, introducing into a cell 25 nM of Peptide of SEQ ID NO: 3 results merely in some bone growth, whereas lesser amount of Peptides of SEQ ID NO: 2, SEQ ID NO: 4, and SEQ ID NO: 7 cause higher level of bone growth. Furthermore, although peptides SEQ ID NOs 1, 5, 6, and 8 resulted in similar degree of bone growth as the peptide of SEQ ID. NO 3, much smaller amounts of these peptides were used. Accordingly, peptide of SEQ ID NO: 3 has minimal osteoinductive potential relative to peptides of SEQ. ID. NOs 1-2 and 4-8. As shown in Exhibit A, peptide of SEQ ID NO: 3 does not include the domain GAPPPADSA shared by peptides of SEQ. ID. NOs 1-2 and 4-8. Accordingly, it can be concluded that the domain GAPPPADSA is responsible for higher osteoinductive potential of peptides of SEQ. ID. NOs 1-2 and 4-8. There is clearly no teaching or suggestion in the prior art that LMPs may own their osteoinductive functionality to a nine amino acid sequence.

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[1] Also, Liu et al. state that it appears that a 36 amino acid sequence of LMP-1 may be responsible for bone formation. It should be noted that the articles is authored by the named inventors of the inventions claimed in the instant application.

Peptides of SEQ. ID. NOs 1-2, 4 and 7-8 do not comprise the amino acid sequence corresponding to amino acids 94-133 of the amino acid sequence of human LMP-1. In fact, these peptides are significantly shorter than 40 amino acids long, ranging from 22 to 30 amino acids. Despite of that, these peptides retain osteoinductive functionality, as shown in Fig. 6 of the instant application.

Given the unpredictable effect that altering the length and/or composition of a protein may have on its stability and functionality, it was far from certain that a peptide other than previously disclosed full length LMP proteins and comprising or consisting the amino acid sequence corresponding to amino acids 94-133 of the amino acid sequence of human LMP-1 would still have osteoindactive activity. It was completely unexpected that peptides significantly shorter than that sequence would still have osteoinductive activity.

The Examiner argues that Hair et al. teaches the peptide of SEQ ID No. 7 because SEQ ID NO. 7 is identical to amino acids 120-149 of SEQ ID No. 10 of Hair et al. SEQ ID No. 10 is a full length LMP-1, which is 457 amino acids long. Where is the teaching or motivation in Hair et al to select this specific sequence out of hundreds of available alternatives? Could one with ordinary skill in the art at the time of invention reasonably expect from the disclosure of Hair et al. that taking a seemingly random sequence of 29 out of 457 amino acids and administering it to a patient would inducing bone formation, proteoglycan synthesis or osteoblast differentiation? The Examiner's argument does not answer these questions. Instead, in making this argument the Examiner completely relies on impermissible hindsight instead of the disclosure of the prior art.

As explained above, it was completely unexpected that peptides 30 amino acids long or less would still be capable of inducing bone formation, proteoglycan synthesis or osteoblast differentiation.

In light of the foregoing, Applicants respectfully request withdrawal of this ground for rejection.

3. Double Patenting Rejections.

Claims 7-9 were rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 of U.S. Patent No. 6858431 ("the '431 patent") in view of Nagahara et al.. Claims 7-9 and 36-38 were also rejected for the same reason over

claims 1-13 of U.S. Patent 6,521,750 ("the '750 patent") in view of Nagahara et al. As set forth above, the instant claims are not obvious in light of the '750 patent or '431 patent in light of Nagahara et. al. Claims 7-9 were rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 10 of U.S. Patent No. 7,504,374 ("the '374 patent").

Applicants have cancelled claim 7, thus rendering this ground for rejection moot.

4. Rejections under 35 U.S.C § 112

Claims 7-15, 21-30 and 36-40 stand rejected under 35 U.S.C § 112, first paragraph, as failing to comply with the written description requirement. Claims 44-49 were added to the rejection.

Again, only independent claims 45, 47 and 49 are still pending in the instant application. These claims were amended to clarify that the fusion peptides are produced by fusion of a protein transduction domain to SEQ ID NO 1, SEQ ID NO 2, SEQ ID NO 4, SEQ ID NO 7, or SEQ ID NO 8. Such peptides were shown to induce bone growth when introduce into cells. (Claim 45). Moreover, from the instant disclosure, a person with ordinary skill in the art would also understand that introducing these peptides into cells as part of the fusion protein also induces proteoglycan synthesis and osteoblast differentiation (claims 47 and 49).

In light of the foregoing, Applicants respectfully request that the Examiner withdraw this ground for rejection.

CONCLUSION

Applicants believe that they have fully responded to the Examiner's concerns, and the claims of the instant application are in condition for allowance. Applicant respectfully requests that any questions concerning this matter be directed to the undersigned at (901) 396-3133. Please charge any deficiency and/or credit any overpayment to Deposit Account No. 132546.

Respectfully submitted,

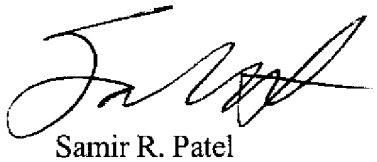

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EXHIBIT A:

SEQ ID 1: APSVSLNKTARPF**GAPPPADSA**
SEQ ID 2: ARPF**GAPPPADSA**PQQNGQPLR
SEQ ID 3: KPQKASAPAADPPRYTFAPSVS
SEQ ID 4: LNKTARPF**GAPPPADSA**PQQNG
SEQ ID 5: ASAPAADPPRYTFAPSVSLNKTARPF**GAPPPADSA**PQQNG
SEQ ID 6: SKPQKASAPAADPPRYTFAPSVSLNKTARPF**GAPPPADSA**PQQNG
SEQ ID 7: **GAPPPADSA**PQQNGQPLRPLVPDASKQRLM
SEQ ID 8: **GAPPPADSA**PQQNGCRPLTNSRSDRWSQMP